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10/030,504	03/04/2002	Andre R. Miserez	0796/66513	9130

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,504	MISEREZ, ANDRE R.	
	Examin r	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,32 and 34-61* is/are pending in the application.

4a) Of the above claim(s) *10 and 37-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Status

1. Claims 10, 32, 34-61 are pending.

Claims 32 and 34-36 are rejected.

Claims 10 and 37-61 are withdrawn from consideration.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Drawings

2. The drawings are now acceptable in view of the corrected sheet

Claim Rejections - 35 USC § 101

3. The rejection of claims 32-34 under 35 U.S.C. § 101 is withdrawn in view of the amendment to include "purified".

Claim Rejections - 35 USC § 112 – Second Paragraph

4. Claims 32 and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 remains vague and indefinite because it is indefinite how a polymorphism comprises SEQ ID NO: 1 or 3. The problem with the claim results in part from the amendment, which now refers to both SEQ ID Nos: 1 and 3, where previously only SEQ ID NO: 3 was referenced. SEQ ID NO: 1 has the wildtype sequence and SEQ ID NO: 3 has the mutant sequence. This is clear from the specification. However,

it is unclear what constitutes a purified oligonucleotide comprising the C10G polymorphism because it is unclear what context is required. As noted before, a polymorphism refers to an alteration in a sequence, and not a sequence itself. So any oligonucleotide with a G contains a nucleotide of the C10G polymorphism with the polymorphic nucleotide. Further, since the claim refers to the change in both SEQ ID Nos 1 and 3, where 1 is wildtype and 3 is mutant, it is indefinite whether the oligonucleotides which embody SEQ ID NO 1 would fall within the scope of the claim. The claim expressly refers to SEQ ID NO: 1, but SEQ ID NO: 1 does not have the G at position 10, though it does have a G at positions 1, 8, 9, 14 and 15 and in the absence of any context requirement, those G could be included in the claim.

Amendment of the claim to "A purified oligonucleotide which is 19 to 30 nucleotides in length and which comprises SEQ ID NO: 3" would overcome this rejection (and would overcome the 112, first paragraph rejections as well). Basis for the 19 nucleotides derives from SEQ ID NO: 3 itself and basis for the 30 nucleotide upper length limitation is found at page 11, line 28 of the specification).

Claim Rejections - 35 USC § 112 – Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

The current claims are drawn to purified oligonucleotides which comprise a "polymorphism characteristic for an increased or decreased risk for hypercholesterolemia in humans" where the polymorphism comprises a C10G change as set forth in "SEQ ID NO: 1 or 3". The sequences being claimed, SEQ ID NO: 1 and 3 are not themselves polymorphism, but rather is a 19 nucleotide oligomer. The specification discloses in figure 1 that there is a single polymorphism in this 19 mer, a G to C change that alters the restriction site of Xmn I. This disclosure does not provide description for all possible C to G polymorphisms in SEQ ID NOs: 1 or 3 which may be associated with an altered risk of hyperchosterolemia.

The problem with the claims remains because no context is provided. The claims therefore encompass virtually any oligonucleotide that has a G, since without contextual sequence every oliognucleotide with a G has the G of the polymorphism.

The definition here, while not entirely functional since a single nucleotide, or G, is required, is substantially functional.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition in claim 32 of a polymorphism associated with hypercholesterolemia which lacks any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the two specific polymorphisms, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a polymorphism in the SREBP-1 gene", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred,

> that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a deletion, without any definition of the particular polymorphisms claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise polymorphisms of the SREBP1 or SREBP 2 genes.

Another issue is whether there is any structure function relationship which correlates the function, hypercholesterolemia, with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the function of hypercholesterolemia. In this case, the answer is no, there is no structure given, other than the two specific polymorphisms, which is associated with hypercholesterolemia.

Conceptually, at minimum a polymorphism is a single nucleotide change in a DNA sequence. It may represent a larger change, including a deletion, an insertion or multiple changes, but minimally consists of a single nucleotide change. To describe such a change, both possible nucleotides at the position of interest must be disclosed.

It is insufficient to describe a polymorphism as, hypothetically, an Adenine at position 57, because this is not a polymorphism, just a sequence. In order to be a polymorphism, the description must state, for example, a Guanosine for Adenine change at position 57. So the description of a sequence is not a description of a polymorphism, since the sequence alone does not provide the structure of the change that IS the polymorphism.

So instant claim 32, for example, provides no description of any polymorphism whatsoever. Further, the specification provides a description of only two polymorphisms. There is no structure in common between the specific nucleotide change in SREBP-1 and SREBP-2. More importantly, there is no structure in common between the specific change at either of the disclosed polymorphisms and any other polymorphism which may exist. This is because there is nothing in common between having a G to A change at position 57 and having a C to A change at position 93 or a G to T change at position 105 or even having a G to A change at position 33 (all of which are hypothetical changes). Even the G to A change at position 33 shares no structural relationship with the G to A change at position 57 because each of these changes occurs in distinct sequence regions, with distinct effects and with no necessary relationship. So there is no common structure between polymorphisms.

The presence and existence of the two polymorphisms in the SREBP sequence does not even necessarily demonstrate that the SREBP receptor itself is necessarily involved in hypercholesterolemia and consequently, the structure of SEQ ID NO: 3 is not necessarily even relevant. These polymorphisms may simply represent markers for

another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in hypercholesterolemia may be tens of thousands of nucleotides distant from the polymorphisms in the SREBP gene.

Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 – Scope of Enablement

7. Claims 32 and 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the two demonstrated polymorphisms in the SREBP gene, does not reasonably provide enablement for all G polymorphisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to polymorphisms in the SREBP gene which are associated with hypercholesterolemia. The invention is is the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass an oligonucleotide which has a G, representing the C10G polymorphism of SEQ ID NO:3, but without any requirement for the contextual sequence. The claims broadly encompasses the polymorphisms in any mammalian patient. This means that the method is broadly drawn to the use, not only of human polymorphisms, but also of sheep, bats, whales or any other mammal. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on hypercholesterolemia.

Claim 36 is separately even more problematic since it includes other undisclosed polymorphisms associated with Alzheimer's disease and hypercholesterolemia but does not provide any structure or identification of these polymorphisms whatsoever.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as hypercholesterolemia. Screening each possible polymorphism in the SREBP genes represents an inventive, unpredictable and difficult undertaking in itself. As shown in the results on page 34, over 3000 human patients were studied. This would require years of inventive effort,

with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) notes with regard to association of mutations studies that larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). So the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for polymorphisms. This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example). Therefore, it is highly

unpredictable whether some currently unknown polymorphism would have any assocation with any disease.

Working Examples

The specification has a working example where two polymorphisms are associated with hypercholesterolemia.

Guidance in the Specification.

The specification did not provide sufficience evidence to demonstrate the association of any polymorphism in SEQ ID NO: 3 with hypercholesterolemia or any other disease. The specification entirely lacks any teaching or discussion of SREBP polymorphisms other than the two disclosed which are associated with hypercholesterolemia.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching gene association studies are highly unpredictable is demonstrated by Lucentini, Wacholder and Ioannidis. The specification provides one with no written description or guidance that leads one to a reliable method where any oligonucleotide with a G will be associated with hypercholesterolemia. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms as diagnostic of

hypercholesterolemia as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the full scope of the claims at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 32, 35-36 are rejected under 35 U.S.C. 102(a) and (b) as being anticipated by Roy et al (Cell (1995) 80:167-178) as evidenced by Genbank Accession No. AC122129 and http://bacpac.chori.org/clones.htm.

Roy teaches synthesis of BAC chromosome libraries and in particular the RPCI 1 library. The RPCI library is also known as RP1, as noted at http://bacpac.chori.org/clones.htm, which states "For instance clone "RP11-103B2" indicates a clone in BAC library "RP11", a.k.a "RPCI-11". Genbank Accession No. AC122129 comprises the sequence of the RP1 clone RP1-253P7. This clone was in the RP1 library that was independently arrayed in 1995 by Roy as noted at page 176,

column 2 (and was commercially available from the BACPAC consortium). Because this clone (which is derived from human chromosome 17) teaches the complete sequence of SEQ ID NO: 3, it meets the requirements of claims 32-36.

With regard to claims 32 and 34, Genbank Accession No. AC122129 shows a sequence alignment

```
Genbank Accession No AC122129  69750 GCACCTAGGGAAAGGCTTC 69732
                                      |||||||||||||||||||
SEQ ID NO: 3                   1      GCACCTAGGGAAAGGCTTC 19
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With regard to claim 34, the sequence of Genbank Accession No. AC122129 inherently comprises an Xmn I site (see sequence above).

With regard to claims 35 and 36, Roy teaches that the oligonucleotide is attached, indirectly, to a solid support (see page 176, where the clones were propagated in microtiter dishes).

10. Claims 32 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Yokoyama et al (Cell (1993) 75:187-197).

Yokoyama teaches a purified oligonucleotide comprising a polymorphism as set forth in SEQ ID NO: 1 (see page 188, figure 1, plasmid pCY22, which has the wildtype SREBP-1 sequence). As noted repeatedly above, the claims lack any specific sequence requirement. In fact, while the claims were treated as requiring a G, the claim does not actually require the G, but is drawn to the polymorphism, and since SEQ ID NO: 1 is explicitly named, can be reasonably interpreted as including SEQ ID NO: 1).

Yokoyama does not meet claim 34 because the wild type sequence lacks an Xmn I site

With regard to claims 35-36, Yokoyama teaches libraries, which are composed of purified nucleic acids on filters and which had the pCY22 clone which comprises SEQ

ID NO: 1 (see page 195, column 1, paragraph 3, beginning "The HeLA"). The filter is a form of a "DNA chip".

Response to Arguments

11. Applicant's arguments filed May 8, 2006 have been fully considered but they are not persuasive.

Applicant argues that the amendment to claim 32 overcomes the 112, second paragraph rejection. While the claim is better, the claim still remains indefinite because the context of the polymorphism is not given in the claim as discussed in the rejection. This is particularly a problem since the claim added SEQ ID NO: 1 to the claim, which is the wild type sequence.

Applicant argues that the 112, first paragraph rejections should be withdrawn because the claims are limited to a particular polymorphism. As noted in the rejection, this is insufficient because the problem with the claims as written is that only the polymorphism is required. So any G containing oligonucleotide, including for example GGGGGGGGGG, comprises the polymorphism. To avoid the written description and enablement rejections, the context is required.

The Roy disclosure is not simply a sequence. The Roy disclosure is the disclosure of an oligonucleotide, in this case a BAC, which is an oligonucleotide that is purified relative to the other library components. That is, the BAC is not in a mixture of all of the BACs, but rather is located at a discrete location on a plate. Therefore, Roy remains applicable.

The new rejection over Yokoyama is necessitated by the amendment to claim 32 to include SEQ ID NO: 1. This addition further confuses the issue of what precise sequence is required by claim 32, which is an oligonucleotide comprising a polymorphism. Since SEQ ID NO: 1 has the wildtype position of the polymorphism, the addition of SEQ ID NO: 1 implies that the claim encompasses this scope.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637

6/8/06